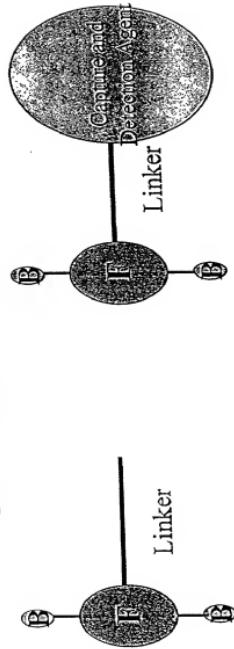


High-throughput Target ID



Library of Bioactive Compounds

Library of Target ID Compounds

1

Use corresponding activity-based probe to identify the biological target

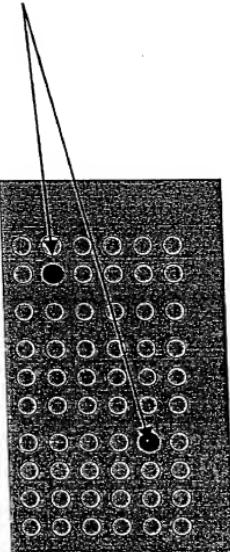
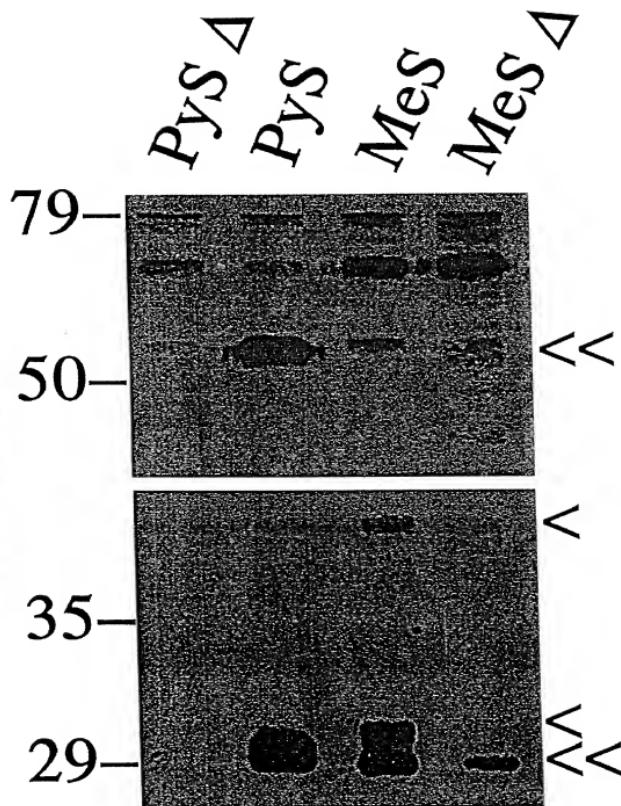
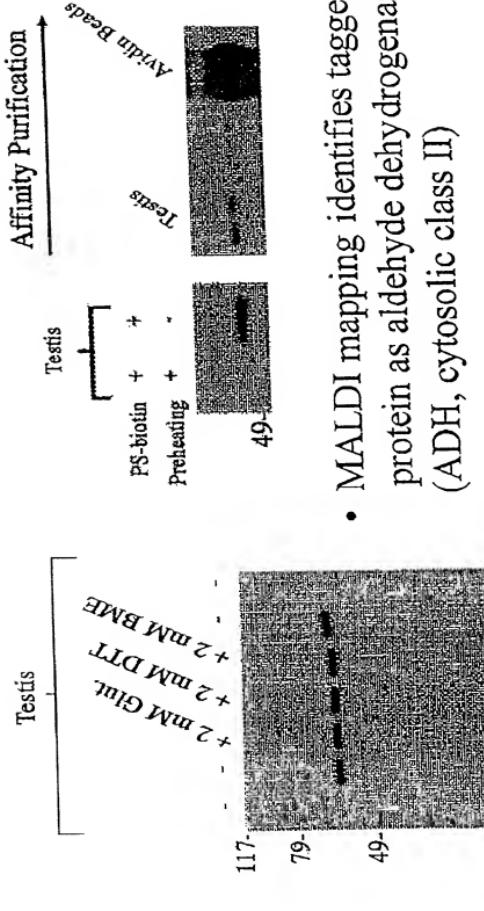


FIGURE 1

FIGURE 2



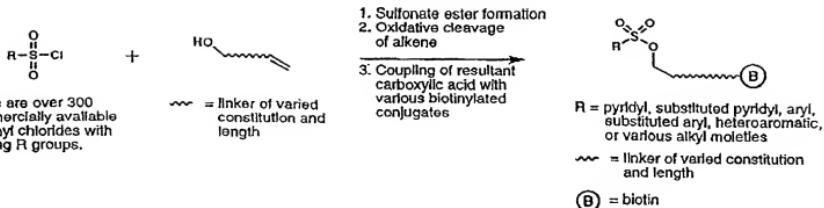
Non-Directed Tagged Library of Sulfonates Identifies Probe for ADH Superfamily of Enzymes



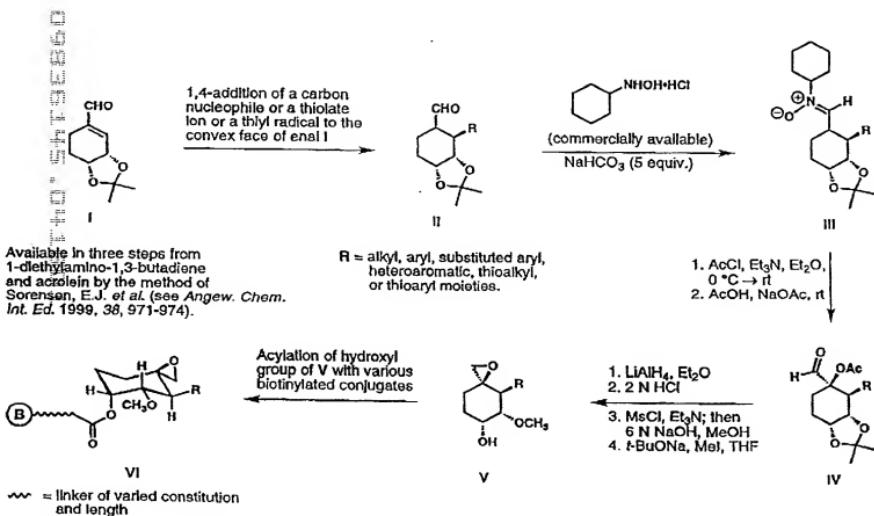
- MALDI mapping identifies tagged protein as aldehyde dehydrogenase (ADH, cytosolic class II)
- 28 ADHs in fly genome
 - Involved in retinoic acid biosynthesis and catabolism of alcohol and chemotherapeutic agents

FIGURE 3

FIGURE 4



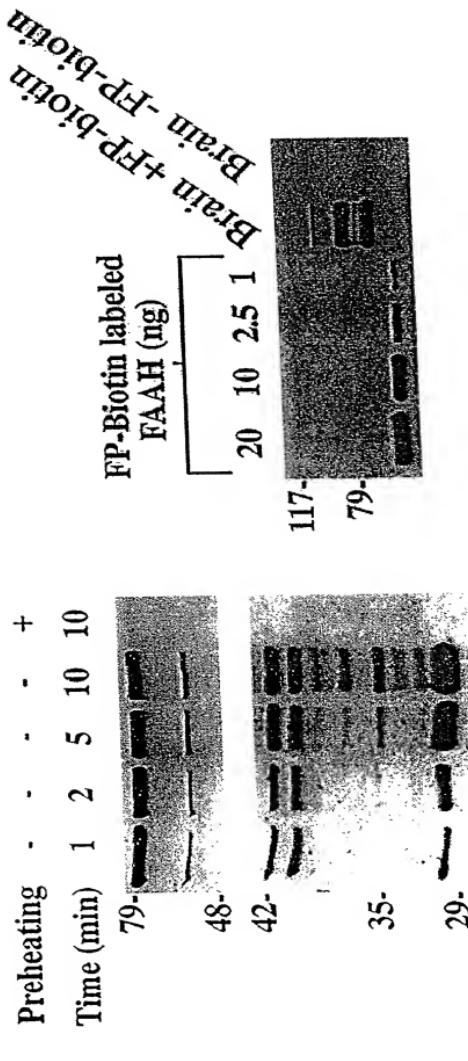
Scheme 1. A pathway for syntheses of various biotinylated sulfonate esters for use in activity-based proteomics studies.



Scheme 2. A strategy for convergent, stereocontrolled syntheses of conformationally well-defined spiroepoxides of type VI. Literature precedent for I → II → III → IV → V can be found in Sorensen, E.J. et al. *Angew. Chem. Int. Ed.* 1999, 38, 971-974. Compounds of type VI are analogs of the metalloprotease (MetAP-2) inhibitor fumagillin and will be employed as covalent affinity agents in activity-based proteomics studies.

FP-Biotin: a kinetic reporter of SH Activity

- The rates at which the majority of SHs react with FP-biotin can be experimentally followed
- FP-biotin readily detects low femtomole quantities of SHs directly in complex cell/tissue proteomes



Utility of Multiplexed probes in identifying Serine Hydrolases

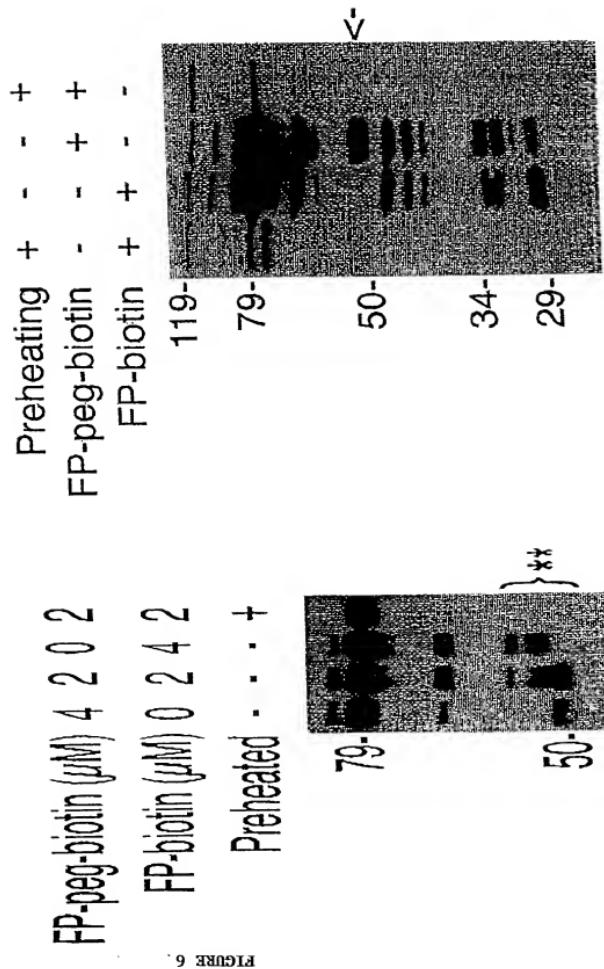


FIGURE 7

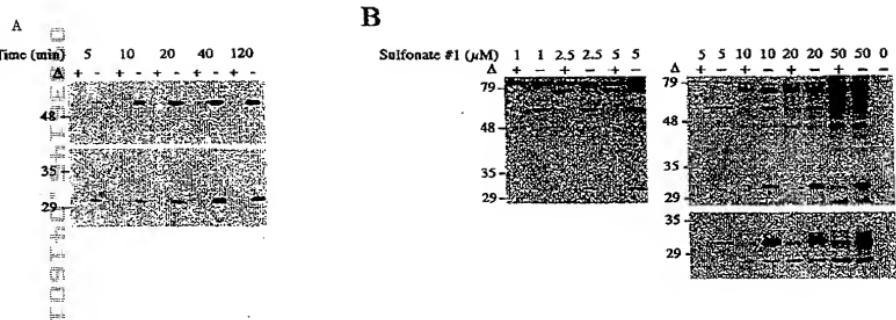
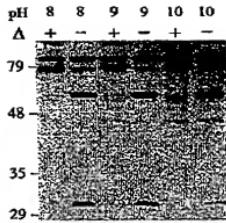
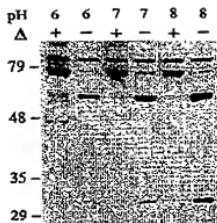


FIGURE 7

TOEPLITZ = SITES 960

C



D

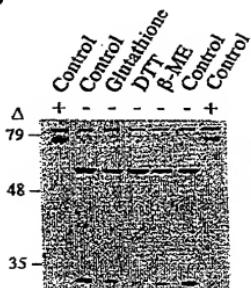


FIGURE 8

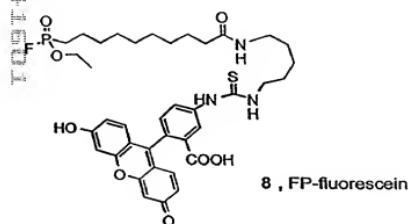
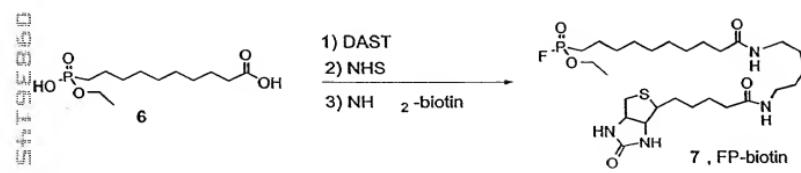
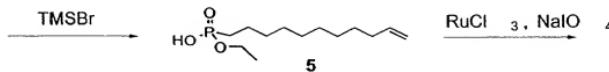
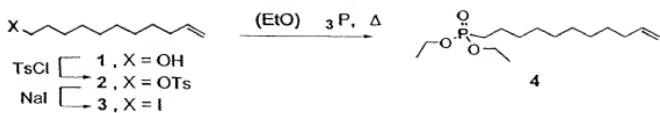


FIGURE 9

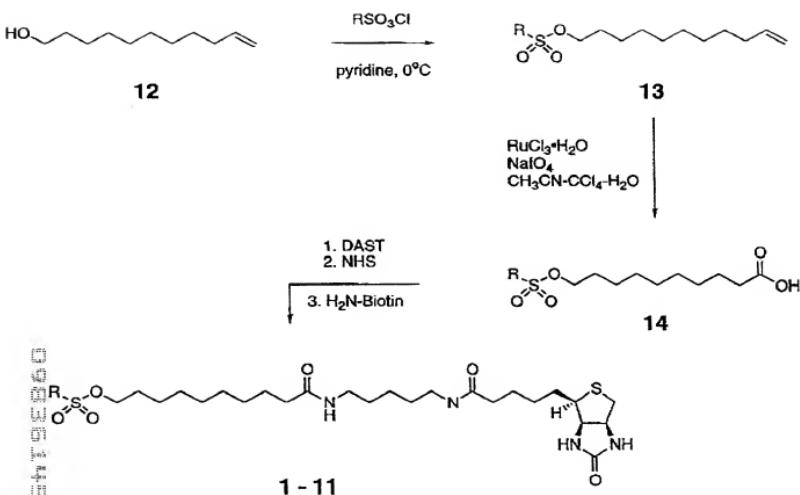


FIGURE 10

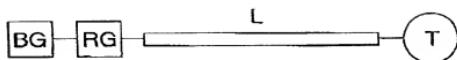
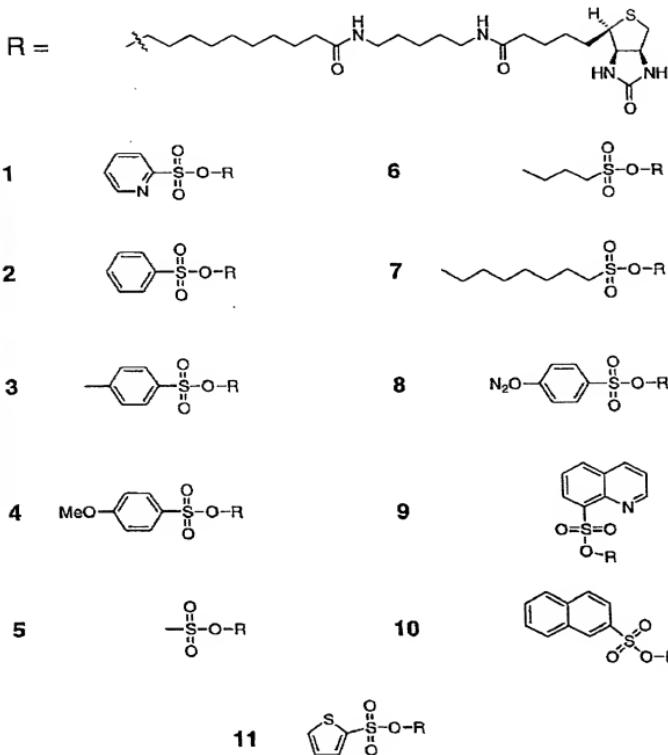
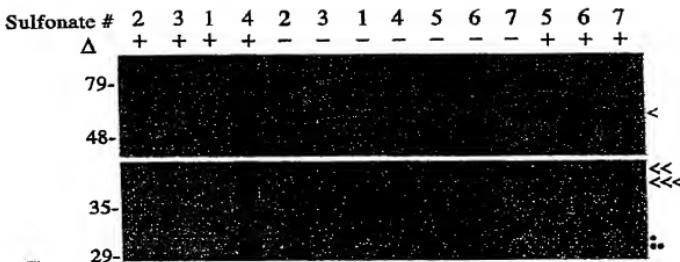
A.**B.**

FIGURE 11

A



B

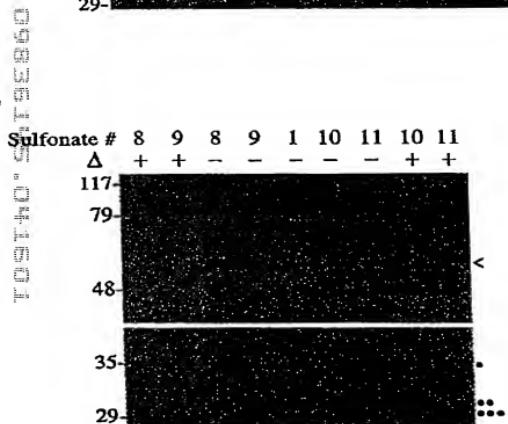


FIGURE 12

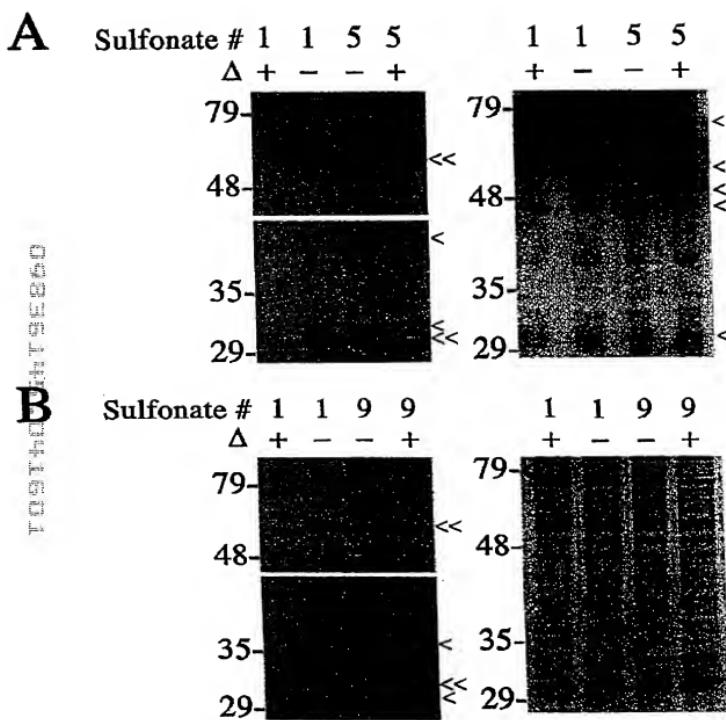


FIGURE 13

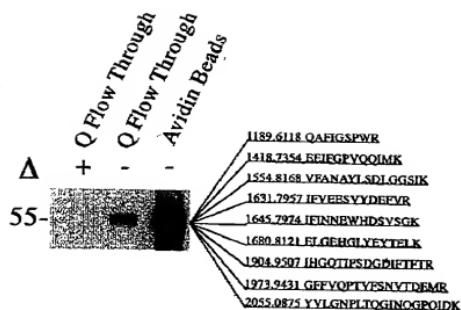
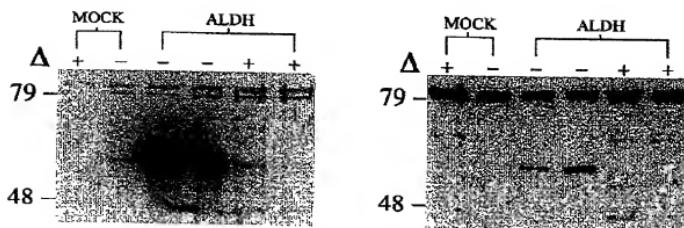
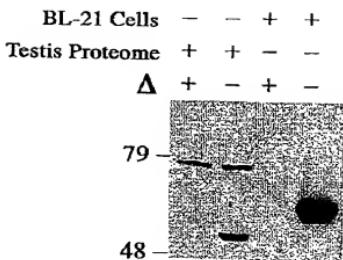
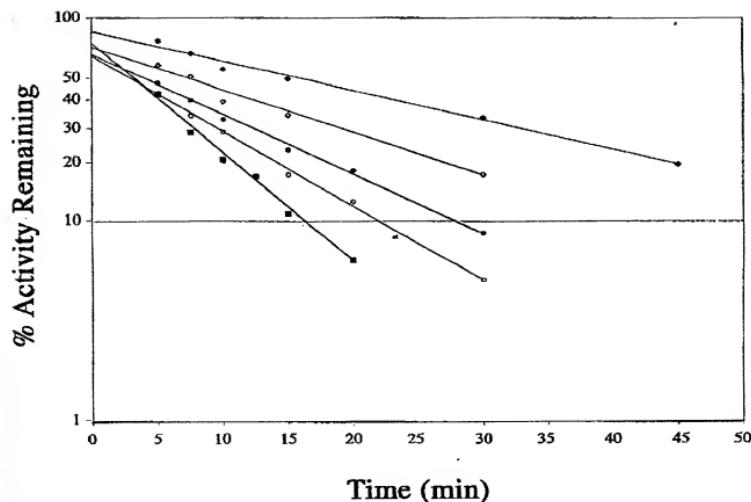
A**B****C**

FIGURE 14

A

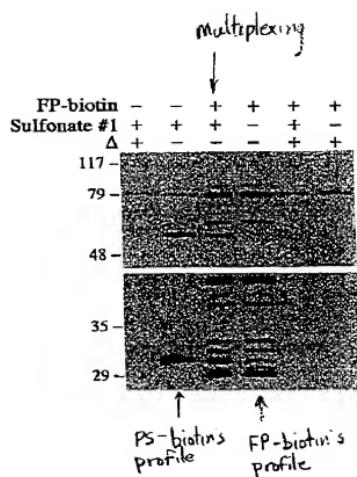


B

Competitor #	-	-	15	17	16	15	17	16
[Competitor (μ M)]	0	0	5	5	5	50	50	50

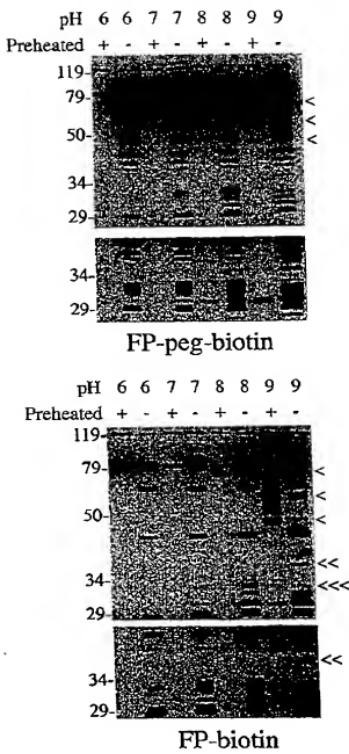


FIGURE 15



1397470 · 54145 · 353850

FIGURE 16



09836145 = 09836146

FIGURE 17

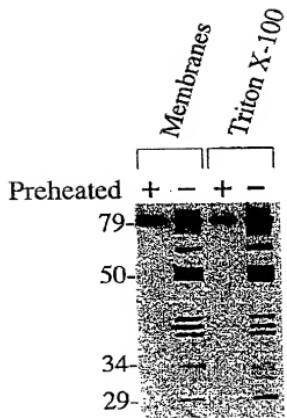


FIGURE 18

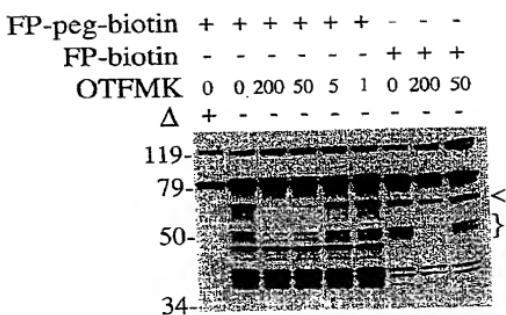


FIGURE 19

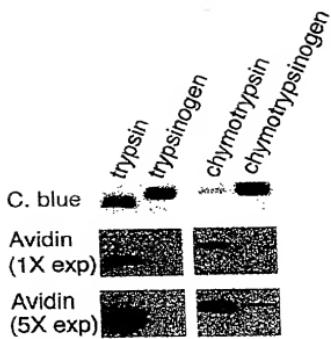
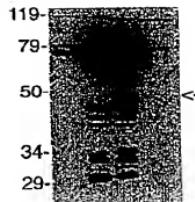


FIGURE 20

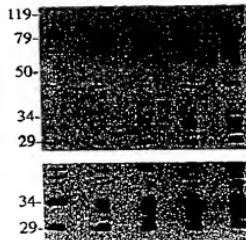
A

	-	-	+	+
FP-peg-biotin	-	-	+	+
FP-biotin	+	+	-	-
Preheated	+	-	-	+



B

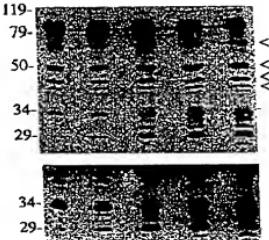
	0.5	1	1	2	2	4	4	8	8
FP-biotin (μ M)	-	+	-	+	-	+	-	+	-
Preheated	-	+	-	+	-	+	-	+	-



09836
001601

C

	0.5	1	1	2	2	4	4	8
FP-peg-biotin (μ M)	-	+	-	+	-	+	-	+
Preheated	-	+	-	+	-	+	-	-



D

	1	2	8
FP-peg-biotin (μ M)	-	+	-



One minute
reaction

FIGURE 21

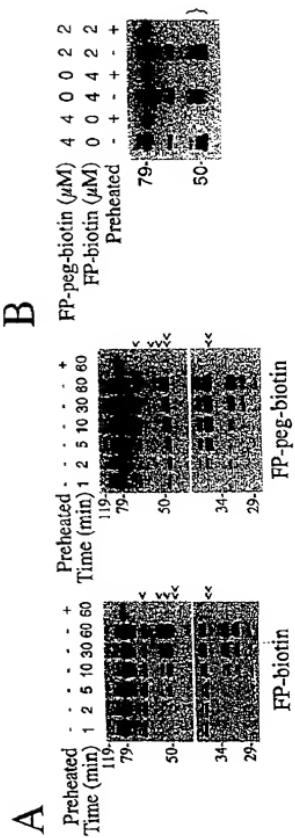


FIGURE 22

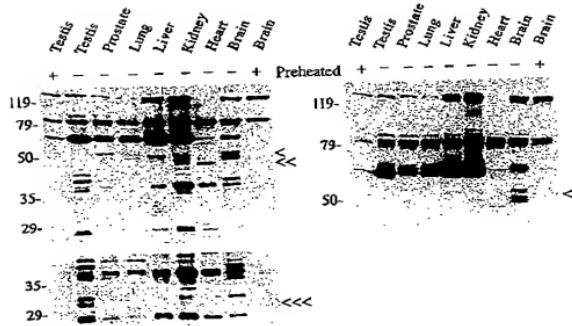
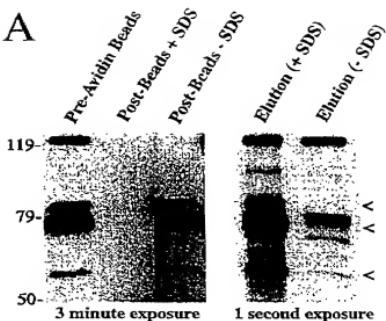


FIGURE 23

A



B

